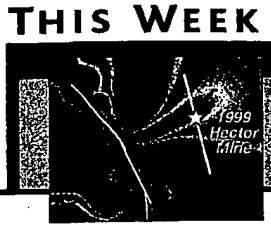


PAGE 656
Shaking up Southern California

659
New Mexico backs Darwin

NEUROSCIENCE

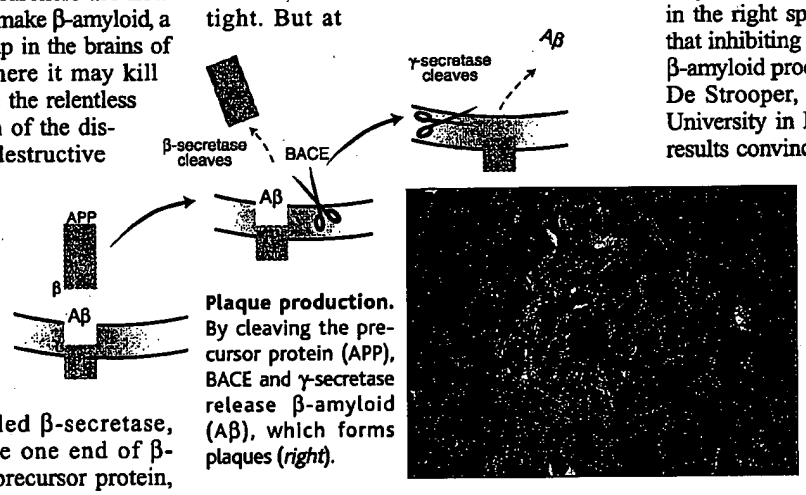
Enzymes Point Way to Potential Alzheimer's Therapies

One way to fight a war is to target the factories where enemy arms are made. New findings, one reported in this issue of *Science* and others due out soon, could make that a fruitful strategy in one of the most frustrating of medical science's battles, the war against Alzheimer's disease. Researchers are now isolating the enzymes that make β-amyloid, a small protein that builds up in the brains of Alzheimer's patients, where it may kill neurons and thereby drive the relentless neurological degeneration of the disease. If amyloid is the destructive agent in Alzheimer's, drugs that target its production could slow or even reverse the disease's course.

The hope is not new. Over the last 5 years, at least a dozen teams have described candidates for an elusive enzyme called β-secretase, which is needed to free one end of β-amyloid from its larger precursor protein, known as APP (for amyloid precursor protein). No candidates have swayed the Alzheimer's research community, and many have already failed to stand the test of time. Now, researchers have new candidates for the β-secretase, one of which is described on page 735 by molecular biologists Martin Citron and Robert Vassar and their colleagues at the biotech company Amgen Inc. in Thousand Oaks, California. This one "is incontrovertible," comments Sangram Sisodia, a β-amyloid specialist at the University of Chicago. "I was floored by the data."

A second β-secretase candidate is due to be reported at this week's annual meeting of the Society for Neuroscience in Miami. Other groups have also identified candidates for the enzyme, known as γ-secretase, that clips the other end of β-amyloid. And even before these candidates were in hand, several companies found compounds that inhibit APP cleavage, which they hope can halt formation of the β-amyloid–containing plaques seen in Alzheimer's brains.

Whether this strategy will stop Alzheimer's disease in its tracks is still a big if, however. While there's good evidence that β-amyloid deposition in plaques causes at least some Alzheimer's cases—for one thing, some relatively rare hereditary cases of the disease have been traced to mutations in APP—the case is not airtight. But at the very least, the new secretase enzymes could settle the dispute, if a β- or γ-secretase inhibitor does in fact help Alzheimer's patients. "Finding the β-secretase enzyme is a very important development, not only for drug development but also for the clues it will give us about [amyloid] biology," says John Durkin, a biochemist at Cephalon in West Chester, Pennsylvania.



Plaque production. By cleaving the precursor protein (APP), BACE and γ-secretase release β-amyloid (Aβ), which forms plaques (*right*).

Hunting for a specific protein-splitting enzyme is extremely difficult, since cells are loaded with hundreds of these proteases. So for their search, the Amgen team decided not to try to isolate the β-secretase protein directly, but instead to look for its gene. The researchers began by introducing large pools of cloned genes into cultured cells that make β-amyloid and then looked to see whether any of these active genes boosted the cells' β-amyloid production. Some genes did, so after eliminating any in which the upturn could be linked to increased APP production, the researchers repeated the experiments until they homed in on a single gene that raised β-amyloid production. The protein encoded by this gene looked extremely promising as a β-secretase candidate.

For one thing, the sequence of the protein indicates that it is in fact a protein-splitting enzyme. But more important, the protein, which the researchers called beta-site APP-cleaving enzyme (BACE), proved to have all the properties expected in a β-secretase. For example, antibody studies showed that it is located in the Golgi apparatus and endosomes, two structures in which APP is known to be cleaved.

In addition, the Amgen team showed not only that the purified enzyme cleaves APP in the right spot for a β-secretase, but also that inhibiting the cellular enzyme decreases β-amyloid production by cultured cells. Bart De Strooper, a neuroscientist at Catholic University in Leuven, Belgium, finds these results convincing. "They have both cell biological evidence and evidence that the purified enzyme acts with the [right] specificity," he says.

But the Amgen enzyme is not the only β-secretase candidate. Elan Pharmaceuticals in South San Francisco has a patent on another one, which is apparently different from Amgen's. At the neuroscience meeting, researchers from pharmaceutical giant SmithKline Beecham plan to describe its own candidate. It's unclear, however, how the SmithKline Beecham enzyme relates to the others. When asked for comment, a company spokesperson would say only that "it's early days" in proving whether they have the right protein.

As for γ-secretase, the second enzyme needed to release β-amyloid from APP, Harvard Medical School neurobiologist Dennis Selkoe and his colleagues suggested in the 8 April *Nature* that presenilin 1, one of two related proteins implicated in some inherited forms of Alzheimer's, may in fact be that enzyme. His latest data, which he will present at the neuroscience meeting, suggest that presenilin 2 as well may be a γ-secretase.

Although other researchers agree that presenilins somehow influence β-amyloid production—its formation is altered when the presenilins are mutated—they think that the proteins play a less direct role. The proteins may, for example, help transport either APP or the secretases to the cell site where APP

CREDITS: (TOP TO BOTTOM) SAM KITTNER; SOURCE: AUCC

CREDITS: (LEFT TO RIGHT) ADAPTED FROM CITRON ET AL., ILLUSTRATION CARIN CAIN; PHOTO: MARTIN ROTKER / PHOTO RESEARCHERS

cleavage occurs. Either way, the presenilins could be potential targets for Alzheimer's drugs, says Selkoe.

Even without knowing the actual identities of any of these enzymes, drug companies have been developing compounds that block their activity. Bristol-Myers Squibb plans to start clinical trials next year on a drug that interferes with γ-secretase activity, though it's not clear if this drug blocks the enzyme itself. Molecular biologist Barbara Cordell says her biotech company, Scios Inc. in Sunnyvale, California, has "both β- and γ- secretase inhibitors and compounds that inhibit [amyloid] by a mechanism we don't understand." Scios has formed partnerships with two large pharmaceutical companies that hope to test some of these drugs in people.

In addition, now that researchers have actual secretase enzymes in hand, they can look for more specific and powerful inhibitors. BACE, for example, is similar to the HIV protease in the AIDS virus, and many compounds have been already developed to inhibit that enzyme.

Alzheimer's researchers hope such compounds will not just prevent new plaques from forming but will also help the brain rid itself of those already present. But whether that can be done without unacceptable side effects remains to be seen. And there's still the big question of whether these drugs will actually make a difference for patients.

Even so, such inhibitors could "provide an excellent opportunity to [affect] Alzheimer's disease in a profound and important way," says Steven Younkin, a neuroscientist at the Mayo Clinic in Jacksonville, Florida. "If we don't isolate the secretases and develop inhibitors, it's totally irresponsible."

–ELIZABETH PENNISI

SCIENCE POLICY

Science Supporter John Porter to Leave Congress

One of the strongest congressional supporters of biomedical research, Representative John Porter (R–IL), announced last week that he will not run for reelection next year. He is the third strong voice for biomedicine who will soon leave a high-profile position.

Porter, chair of the House appropriations subcommittee that drafts the annual funding bill for the National Institutes of Health (NIH), made the surprise announcement on 12 October. After 21 years on Capitol Hill, Porter told reporters, he wants to pursue "other opportunities and challenges." He's one of a handful of Capitol Hill leaders who have worked to put the NIH budget on a path toward doubling between 1999 and 2003. Porter played a pivotal role in 1995, for example, when a draconian plan drawn up by the new Republican-led budget committee proposed a 5% cut in NIH funding for each of the next 5 years. Porter ushered a delegation of researchers and biotech executives into the office of then–Speaker of the House Newt Gingrich (R–GA) to make a plea for sparing biomedical research. Afterward, NIH got a 5.7% increase, and Gingrich became a research champion, too.

Retiring. Representative John Porter.

Since then, Porter has spoken out several times about his frustrations in dealing with an increasingly fractious federal budget process. Porter's press officer, David Kohn, says his own view is that the "tenor and atmosphere" of congressional debate has become more acrimonious and that his boss seemed to grow tired of the "continual battles with the right wing of his party" over gun control, abortion, and the environment. Kohn adds, however, that new rules adopted by the Republican leadership in 1995 require Porter to step down as chair of the Labor, Health and Human Services, and Education Subcommittee in any case after 2000, and "it was the right moment for a change." There's no "hidden motivation," Kohn says: Porter really does want to spend more time with his children and grandchildren.

Porter's decision to step out of national politics comes on the heels of similar actions by two other key players in biomedical politics. NIH director Harold Varmus revealed last week that he will resign in December to become president of the Memorial Sloan-Kettering Cancer Center in New York City (*Science*, 15 October 1999, p. 382). And Senator Connie Mack (R–FL)—another advocate of doubling NIH's budget by 2003 and a member of the Senate Appropriations Committee—announced in March that he will not run for reelection in 2000.

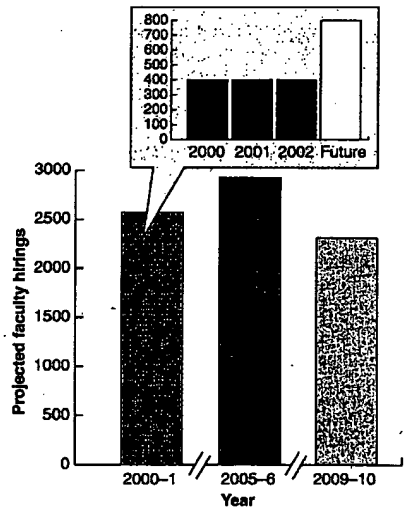
It might not be worrisome if just one of these figures were leaving, says Michael Stephens, lobbyist for the Federation of American Societies of Experimental Biology. But to have all three depart at the same time, he says, "could create a real problem" by depleting the ranks of officials who care about biomedical research. –ELIOT MARSHALL

CANADIAN UNIVERSITIES

Massive Hiring Plan Aimed at 'Brain Gain'

OTTAWA—Canadian universities will soon be turned loose on a massive shopping spree for scientific talent. Prime Minister Jean Chrétien last week unveiled a US$205 million program to create 2000 new research chairs, calling it a "plan for brain gain" aimed at reversing a flow of talent to the United States. University officials applaud the initiative, even if it derives more from a desire to outflank political foes than to strengthen academic research.

The issue of "brain drain" is a political hot potato in Canada. Business leaders have



Sitting pretty. Canada's plan to fund 2000 research chairs (inset) will help universities cope with projected vacancies from retirement and rising enrollment.

CREDITS: (TOP TO BOTTOM) SAM KITTNER; SOURCE: AUCC